Original article

Oral examination: a screening tool for HIV infection?

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Objective: To estimate the predictive values for HIV infection of diagnosis of oral manifestations of the infection.

Method: Prevalence of oral manifestations was compared in cross sectional blinded clinical examinations of homosexual men attending a genitourinary medicine clinic. Data were extrapolated to populations in England and Wales based on estimates of the prevalence of HIV infection.

Results: Data were analysed for 572 HIV infected and non-infected men (312 and 260 respectively). Positive predictive values for erythematous candidiasis, hairy leucoplakia and pseudomembranous candidiasis were greater than 0.96 at the genitourinary medicine clinic and are estimated to be greater than 0.72 among homosexual men in London.

Conclusions: Clinical diagnoses of mucosal lesions *alone* are poor predictors of HIV infection but are useful when used in conjunction with a social history to establish if there are risk factors for infection.

(*Sex Transm Inf* 1998;74:345–348)

With the advent of more effective treatments for HIV infection, there are distinct advantages to its earlier detection, not only in those infected but also to the unborn children of pregnant women with HIV.[1–3] Screening people for HIV might facilitate earlier diagnosis of the infection in time for more effective management of the disease.

Screening can only be justified if there is an effective and available intervention and if the test is valid and acceptable to the population. In addition, the screening should not have excessive adverse psychological and ethical effects.

Examination of the mouth is a simple, non-invasive procedure which few people find unduly unpleasant. Oral lesions are common in HIV disease and have long been recognised as the first manifestation of the infection.[4–6] Earlier research has associated these oral diseases with HIV infection but has not comprehensively considered the ability of the diagnosis of oral disease to predict the presence of HIV.[7–13] The aim of this study was to assess the ability of diagnosis of oral mucosal lesions to predict HIV infection in populations of differing HIV prevalence.

Method

A convenience sample of homosexual men attending a genitourinary medicine clinic in London was examined during a 15 month period. All were between 18 and 65 years of age, had 20 or more teeth, did not have a history of injecting drug use, and did not have medical conditions which precluded dental examination. Men meeting the inclusion criteria were identified by the clinic staff and recruited to the study. Men who had injected drugs were asked not to take part. All participants gave written consent.

To allow the examiner to be blinded to the HIV status of participants, clinical examinations took place in a separate room and participants were asked not to reveal information about their status to the examiner. A single, dentally qualified examiner with 10 years' experience treating patients with HIV was used throughout the study (PR). Participants were examined with a dental mirror while lying on a couch with their mouths illuminated by a Daray portable halogen lamp held 60 cm away. The presence of mucosal diseases associated with HIV infection was recorded for each participant using the presumptive diagnostic criteria devised by the US collaborative group (table 1).[14] Diagnoses were made on clinical appearance alone.

Medical records were viewed 1 month after examination and again at the end of the 15 months for those of indeterminate HIV status. The prevalence of oral lesions was compared in men with and without HIV and the positive and negative predictive values (PPV and NPV) and likelihood ratios (LR) for HIV infection were calculated.

The PPV, NPV, and LR are used to assess the usefulness of a test. The LR is calculated as the post-test odds divided by the pretest odds and measures the ability of a positive test result to increase the likelihood that a subject has the disease. It does not describe the likelihood of disease itself but has the advantage that it is not dependent on the prevalence of the disease. The PPV is the proportion of those with a positive test result (that is, an oral lesion) who have the disease and the NPV is the proportion of those who test negative who do not have the disease. The PPV is dependent on the prevalence of the characteristic in the population. Data were extrapolated to other populations in contingency tables using estimates of the prevalence of the disease and known sensitivity and specificity data to complete the tables.[15] This is expressed mathematically as Bayes's theorem.[16] PPVs were derived for adults in England and Wales and for homo-

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Table 1   Diagnostic criteria for oral manifestations of HIV infection[14]

Erythematous candidiasis
Erythematous macular patches on mucosal surfaces. When dorsum of tongue is involved area is depapillated
Pseudomembranous candidiasis
Yellow-white loosely adherent (wipable) plaque located anywhere in the mouth
Kaposi's sarcoma
Brown, red, blue or purple macule, papule, or nodule. Has predilection for hard palate and attached gingiva but can appear on other mucosal sites
Oral hairy leucoplakia
Vertically corrugated, slightly elevated white surface alteration of lateral or ventral tongue margin that does not wipe off. May also be seen at other sites, usually in conjunction with tongue lesions
Gingival ulceration
Destructive lesions of marginal gingiva characterised by soft tissue ulceration and necrosis. Forms of gingival ulceration were aggregated to increase diagnostic reliability
Mucosal ulceration
A composite criterion including any interruption of the oral mucosa not attributable to trauma. Forms of gingival ulceration were aggregated to increase diagnostic reliability

sexual men in London and in England and Wales using the sensitivity and specificity data collected at the genitourinary medicine clinic.

Results

A total of 794 men were examined between September 1993 and December 1994. Of these, 260 had tested negative for HIV antibodies in the year preceding or at any time since the examination and 312 men were HIV antibody positive. The remaining 222 did not meet either criterion, were regarded as untested, and excluded from the analysis.

The men with HIV tended to have advanced HIV disease. CD4 lymphocyte counts were available for 276 of whom 37.8% had a count of less than 200 cells $\times 10^6/l$ and 71 had had an AIDS indicator condition.

Overall, mucosal lesions were seen in 59.6% of the men with HIV and 6.5% of those without (table 2). The PPVs for the three most common oral manifestations: erythematous and pseudomembranous candidiasis and oral hairy leucoplakia (EC, PC, and OHL respectively) were 0.96 or greater but the NPVs for specific lesions were 0.6 or less.

The data for men with HIV were stratified by severity of HIV disease. Mucosal disease was seen in 73.2% of the 71 men with an AIDS indi-

cator condition. The PPV for diagnosis of any oral disease was 0.75 and the PPVs for EC, PC, and OHL were 0.79, 1.00, and 0.90 respectively. Among the 241 men without AIDS mucosal lesions were seen in 55.6%. The PPVs for diagnosis of any oral disease, EC, PC, and OHL were 0.89, 0.96, 1.00, and 0.96 respectively.

Among adults in England and Wales the prevalence of HIV infection is approximately 0.09%. Using the recent seroprevalence estimates of Petruckevitch and colleagues and the estimates of the denominator populations used by Giesecke and co-workers the prevalence among homosexual men in London and outside London is 8.7% and 4.4% respectively.[17 18] The PPVs would be expected to be much lower in the adult population but the three most common lesions have PPVs greater than 0.55 among homosexual men in England and Wales and greater than 0.70 among homosexual men in London (table 3).

Discussion

In this study clinical diagnosis of disease of the oral mucosa detected 60% of men with HIV from a group of 572 homosexual men. Overall, 92% of those thought to have HIV, based on their oral mucosal diagnosis, did so but the PPV was greater than 0.96 for the three most common lesions: erythematous and pseudomembranous candidiasis and oral hairy leucoplakia. The sensitivity of the screening was equivalent to the prevalence of lesions in men with HIV. Since 40% had healthy mouths the sensitivity was only 60% and the NPVs were relatively low. At first glance it might be concluded that oral examination is not an ideal tool for screening for HIV as there are a significant number of false negatives. In the general population, where the prevalence of HIV is low, clinical diagnoses of mucosal lesions *alone* are poor predictors of HIV infection (table 3). The low PPVs at these prevalences indicate increased false positive results (that is, 1 − PPV). The PPVs increase if used with a social history to identify risk factors for infection. Only 2.6% of people in England and Wales with mucosal lesions resembling OHL will have HIV but if the person is a homosexual male the PPV rises to 57.4%. In London the PPV is 73.8%.

The predictive values of the diagnoses also increase if other causes of the lesions are excluded in a medical history. Oral candidiasis occurs only in the presence of predisposing factors. Local factors include denture wearing, xerostomia, and topically applied medications. Systemic factors include pregnancy, iron and vitamin deficiencies, and use of broad spectrum antibiotics.[19] Likewise, there are many causes of leucoplakia of the tongue including tobacco use, physical trauma, and lichen planus. However, any white patch in the mouth should be investigated carefully because of the risk of malignancy and laboratory confirmation of the HIV associated diagnoses would increase the PPVs still further.

The findings of this study are compatible with those from other research. Likelihood ratios can be calculated from other studies which have compared the prevalence of oral

Table 2   Oral lesions in men with and without HIV, positive predictive values, and likelihood ratios

	HIV+ve n (%) (n=312)	HIV−ve n (%) (n=260)	PPV	NPV	LR (95% CI)
Any mucosal disease	186 (59.6)	17 (6.5)	0.92	0.66	9.1 (5.4–15.4)
Erythematous candida	84 (26.9)	3 (1.1)	0.96	0.53	23.3 (7.2–75.0)
Pseudomembranous candida	36 (11.5)	0 (0)	1.00	0.49	∞
Hairy leucoplakia	138 (44.2)	4 (1.5)	0.97	0.60	28.7 (10.5–78.6)
Kaposi's sarcoma	14 (4.5)	0 (0)	1.00	0.46	∞
Mucosal ulceration	20 (6.4)	6 (1.9)	0.80	0.47	3.3 (1.22–8.9)
Gingival ulceration	10 (3.2)	4 (1.5)	0.71	0.46	2.08 (0.6–6.7)

PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; CI = confidence interval.

Table 3   Positive predictive values of oral lesions for HIV disease in populations of estimated HIV seroprevalence

	Adults, England and Wales	Homosexual men, London	Homosexual men outside London
Any mucosal disease	0.008	0.467	0.296
Erythematous candida	0.022	0.720	0.552
Pseudomembranous candida	1.000	1.000	1.000
Hairy leucoplakia	0.016	0.738	0.574
Kaposi's sarcoma	1.000	1.000	1.000
Mucosal ulceration	0.003	0.243	0.134
Gingival ulceration	0.002	0.169	0.072

Table 4   Likelihood ratios for oral lesions to predict HIV infection in different populations

	Any lesion	Candida	EC	PC	OHL	KS
Homosexual men, US[7]	4.2	14.6			12.9	∞
Men and women, Tanzania[8]	13.8		10.3	8.7	45.2	
Homosexual men, US[9]			3.5	97.4	69.1	∞
Transfusion recipients, Zaire[10]				5.4		
Homosexual men, US*[11]				3.9–8.7		
Women, US[12]	8.4	∞	∞	∞	5.65	
Homosexual men, US[13]			4.74	∞	∞	
Injecting drug users, US[13]			6.7	7.1	2.1	

*Based on self reported "thrush" at two different stages in a cohort study.
Candida = some studies have not distinguished the different forms of oral candidiasis; EC = erythematous candidiasis; PC = pseudomembranous candidiasis; OHL = oral hairy leucoplakia; KS = Kaposi's sarcoma.
∞In some studies some lesions were not seen in participants without HIV. In these circumstances the LR is theoretically infinity but this should be interpreted with care.

diseases in participants with and without HIV (table 4). The findings of some of these studies where specific lesions were not seen in participants without HIV should be interpreted with care (that is, the LR is theoretically infinity). However, the oral lesions most often seen in HIV infection (EC, PC, and OHL) consistently predicted HIV infection in populations of men and women with different routes of transmission and stages of HIV disease even though the studies where conducted under different circumstances with different diagnostic criteria.[7–13] Research on Italian haemophiliacs with HIV also suggests that oral disease may predict HIV infection but likelihood ratios cannot be calculated from the data presented.[20]

Oral examination is a cheap, simple, and non-invasive procedure and may have a place especially in screening populations at greater risk of HIV, particularly those attending genitourinary medicine clinics. In England and Wales approximately 60% of the adult population attends the dentist for regular check ups and there are well established routes of referral for patients with mucosal disease, where a firm diagnosis can be made.[21] These findings may also be useful to general medical practitioners whom patients often attend with oral mucosal disease. If diagnosis of mucosal disease also predicts HIV infection in women it may be useful in antenatal screening of women so that zidovudine can be used to reduce vertical transmission.[1] It is likely that HIV testing will become part of routine antenatal screening in developed countries such as the United Kingdom. Oral examination might be appropriate as part of antenatal screening in those countries which can provide zidovudine to pregnant women but are unable to undertake routine serological HIV screening.

If medical staff are to screen for oral manifestations of HIV infection they will need training to identify the lesions. In one study physicians did not detect more than 80% of the cases of erythematous candidiasis diagnosed by dentists.[13] As the authors remarked, erythematous candidiasis is often ignored in research and texts produced by physicians and this is of some concern since it is one of the most common oral changes seen in HIV infection.

The high PPVs observed in this study suggest that the US collaborative group criteria are valid.[14] Newer diagnostic criteria have been introduced and are widely used.[6] The two sets of criteria have similar face validity and it is unlikely that the results of this study would have been different if the EC-Clearinghouse criteria had been used.

Anecdotal reports suggest that new HIV therapies have reduced the prevalence of mucosal diseases in the infection. However, these therapies will not affect the prevalence of disease in people as yet undiagnosed. Indeed, the increased use of combination regimens makes a study of this kind more difficult.

These findings should be interpreted cautiously. The convenience sample overrepresented people with HIV and the PPVs are correspondingly high. Although the data could legitimately be extrapolated to populations with lower prevalence it is possible that errors were introduced. Other aetiological factors may have been relatively underrepresented in the sample. Diagnostic test studies are prone to sampling bias if the population studied has severe disease and prone to measurement error if the examiner is not blinded to the status of the subjects. Sampling bias was accounted for in this study by excluding patients with AIDS (who would not need to be screened). This had very little effect on the PPVs and the mucosal diagnosis remained a useful screening test even for men with earlier HIV disease. It is likely that the examiner would have been "partially sighted" to the HIV status of participants with other symptoms of the disease. Unblinding is likely to be more common in late disease and was assessed by comparing the PPVs in men with and without AIDS. Oral disease was more common in men with AIDS but its predictive value was lower due to the lower prevalence of AIDS in the sample.

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Peyronie's disease

Historical vignette

The combination of pain and deformity on erection and a palpable penile mass were mentioned by 16th and 17th century anatomists such as Vesalius and Falloppio, but are now firmly linked with the name of François de la Peyronie (1678–1747). The son of a master barber surgeon, he became chief surgeon to Louis XV of France, and "guardian of the rights and privileges of surgery in the Kingdom." In 1743, in *Mémoires de l'Academie Royale de Chirurgerie,* he published a report "on some obstacles to the natural ejaculation of the semen." In the course of this he described in detail five cases in which nodules occurred in the corpora cavernosa. "If one of these is situated towards the middle of the right corpus cavernosum the penis, instead of being erected in a straight line, will describe an arch whose curvature is on the right side... .These hardnesses are not dangerous, but they impede erection and ejaculation and may thereby cause sterility."

Clinicians in France and elsewhere confirmed the clinical features of these "plastic indurations," but there was little agreement on their cause. Peyronie himself believed that they were a sequel to a venereal infection such as a gonorrhoeal discharge or any type of syphilis. Writing in 1840, Ricord proposed four causes, based on 20 cases he had seen: firstly, gummatous syphilitic induration, which he thought was the commonest; secondly, penile inflammation, mostly secondary to blennorrhagia; thirdly, penile trauma; and fourthly, a small group of unknown aetiology. Most contemporary venereologists, including Fournier, Vidal, and Acton, accepted Ricord's views without question. But Kirby, a physician practising in Dublin, expressed another opinion. In some of his patients with Peyronie's disease he had noted evidence of gout and of the fibrosis of the palmar aponeurosis and tendon sheaths previously described by Dupuytren. He concluded that the penile lesions were one component of an "arthritic diathesis." Kirby's opinion was widely criticised, particularly in France, and in the following years continental surgeons continued to favour either venereal infection, or trauma causing ruptures within the cavernosal tissue, as the cause of most cases. It was observed that some patients were diabetic, and it was suggested that this might be an occasional cause. These ideas of a connection between induration of the corpora cavernosa, Dupuytren's contracture, and diabetes slowly spread. The English surgeon Sir James Paget, writing in 1880, compared "the thickening and contraction of the palmar aponeurosis and the induration of parts of the corpora cavernosa which frightens patients into thinking they have cancer." A few years later Mauriac referred to a "chronic inflammation affecting areas of erectile tissue resulting in thickening of the walls of the alveoli, the cavities filling with a fibrinous exudate." Today this idea, together with genetic and traumatic factors, is alone still seriously considered, although how it causes the clinical features of Peyronie's disease is uncertain.

Like its aetiology, treatment of the disease has always been problematical. Peyronie, although believing that it was often the result of venereal infection, was surprised when it failed to respond to mercury. He made many fruitless attempts to find a cure, but "seeing a great many persons were averse to continue the remedies, I grew weary myself of prescribing them." He then found by chance that bathing with "the waters of Barège" (a medicinal spring) seemed to be effective. Subsequently, physicians used this material, mercurial frictions, iodine ointment, and many other agents, all without success. There is perhaps a note of despair in a case report which appeared in the *Lancet* in 1851: "I prescribed leeches, blisters, mercurials, tartar emetic, iodine ointments, fomentations, cold lotions, even ice, with calomel, opium, salines, iodide of potassium, sarsparilla—in short, all the remedies which would naturally occur to me in the management of such a case." There were occasional successes, the penile abnormalities reverting to normal, but it is likely that this was due to the spontaneous improvement which was known to occur. This was probably also the case with two forms of treatment which became popular in recent times—vitamin E (tocopherols) and potassium aminobenzoate. Vitamin E was tried either by local injection, systemically or in combination, sometimes with corticosteroids as well. Although good results were sometimes reported there is little scientific evidence of its value. Potassium aminobenzoate (Potaba) has been used in the treatment of various disorders associated with excessive fibrosis, but its therapeutic value, even in prolonged dosage, is doubtful. These agents were in reality little more than placebos. Surgical treatment for Peyronie's disease was avoided in the 19th century, but a report by Merle in 1899 is often quoted. A soldier received a bullet wound in the right corpus cavernosum. After healing, the penis showed a considerable curvature to the right, and a surgeon thought of inducing an analogous lesion on the other side. Two deep incisions were made in the substance of the left corpus cavernosum, and wicks of lint were inserted to encourage suppuration. Two adherent and depressed scars resulted, and after healing the result was excellent, the curve which had affected the penis during erection being now almost absent. Merle suggested that treatment by contralateral plication to reduce the effect of the deviation might be effective. In essence, this observation forecasted the technique of plaque excision with dermis grafting which was described half a century later. Other and improved surgical procedures were to follow.

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